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Histidine 440 controls the opening of colicin E1 channels in a lipid-dependent manner

Alexander A. Sobko *, Tatyana I. Rokitskaya, Elena A. Kotova

A.N. Belozersky Institute of Physico-Chemical Biology, Moscow State University, Moscow 119991, Russia

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ABSTRACT

The in vitro activity of many pore-forming toxins, in particular, the rate of increase in the membrane conductance induced by the channel-forming domain (P178) of colicin E1 is maximum at an acidic pH. However, after P178 binding at acidic conditions, a subsequent pH shift from 4 to 6 on both sides of the planar bilayer lipid membrane caused a large increase in the trans-membrane current which was solely due to an increase in the number of open channels. This effect required the presence of anionic lipid. Replacing the His440 residue of P178 by alanine eliminated the pH-shift effect thereby showing that it is associated with deprotonation of this histidine residue. It was concluded that alkalinization-induced weakening of the electrostatic interactions between colicin and the membrane surface facilitates conformational changes required for the transition of membrane-bound colicin molecules to an active channel state.

1. Introduction

In vitro activity of the channel-forming colicins is largest at an acidic ambient pH, in particular the activity of colicin E1 is maximum at pH less than 5 [1]. This acidic pH dependence has been ascribed to increased binding of colicin molecules bearing a greater net positive charge to the negatively charged phospholipid surface of the membrane [2] and protein unfolding which involves a massive conformational change [3]. Such acidic pH dependence in vitro is well known, not just for the toxin-like channel-forming colicins, but is also characteristic for the in vitro activity of toxins such as diphtheria [4–8] and anthrax [9] toxins, staphylococcal alpha-toxin [10], and exotoxin A [11]. An approximately monotonic dependence of colicin binding on acidic pH does not, however, explain the discovery that the channel activity of colicin E1 is not monotonically dependent on the magnitude of the negative surface potential of the target membrane surface. To the contrary, the channel activity of colicin E1 is maximal at a value of the membrane surface potential, Ψ°, approximately equal to −60 mV, the surface potential of phospholipid membranes containing 20–30% monovalent anionic lipid in 0.1 M ionic strength. The decreased channel activity at larger negative values of Ψ° was ascribed to electrostatic interactions that are strong enough to limit the conformational freedom required for the insertion of the colicin from its surface-bound state into the membrane bilayer [12].

Protein–lipid interactions are a major determinant in the formation of protein-induced pores in lipid membranes. Considerable evidence has been obtained to show that colicin E1 forms toroidal protein–lipid pores [13–17]. Both channel activity and single-channel characteristics of these pores in model membranes have a pronounced dependence on lipid properties [13,15]. The inhibitory effect of calcium ions on the colicin E1 channel activity observed only with negatively charged phospholipid membranes was explained in terms of the toroidal model, by Ca-induced modulation of spontaneous lipid curvature [18]. Recent results [19] suggest that the hydrophobic helical hairpin, helices VIII–IX, near the C-terminus of the colicin, could be involved in the toroidal pore formation of colicin E1, by perturbing the lipids and facilitating the insertion of the other, more hydrophilic, helices that will form the pore.

The present study describes a large increase in colicin channel activity caused by an alkaline-directed shift in pH after colicin was initially bound to membranes at pH 4. The presence of negatively charged lipid in the membrane was required for this effect. The increase in the colicin channel activity was manifested in a large stimulation of colicin-mediated electric current across BLM. The results of the present study apparently imply that two stages in the process of the channel formation of colicin E1, i.e. membrane binding and pore-opening, exhibit quite different pH dependences, with the second stage being activated at an alkaline pH in the presence of acidic lipids. To define the role of certain amino acid residues in the phenomenon observed, we performed site-directed mutagenesis which provided unambiguous evidence in favor of the participation of His440 in the pH-shift effect.

Abbreviations: BLM, bilayer lipid membrane; P178, 178-residue C-terminal colicin E1 polypeptide prepared by thermolysin proteolysis; DPhPC, 1,2-diphytanoyl-sn-glycero-3-phosphocholine; DPhPG, 1,2-diphytanoyl-sn-glycero-3-[phospho-rac-(1-glycerol)] (sodium salt); DOPC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; DOPG, 1,2-dioleoyl-sn-glycero-3-[phospho-rac-(1-glycerol)] (sodium salt); SDS, sodium dodecyl sulfate; cmc, critical micelle concentration

* Corresponding author. Fax: +70 95 939 31 81.
E-mail address: sobko@genebee.msu.ru (A.A. Sobko).

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2. Materials and methods

2.1. Peptide preparation

The channel-forming domains of the wild-type (P178) and mutant (H427/440A, H440A and H427A) forms of colicin E1 were generously gifted to us by Stanislav D. Zakharov and Mariya V. Zhalnina (Purdue University, West Lafayette). The 178-residue C-terminal colicin E1 channel polypeptide, P178, was prepared by thermolysin proteolysis of intact colicin E1 [20]. The mutations H427/440A, H440A and H427A were done in colicin E1 cloned into a pT7-7 plasmid. Proteins were expressed in IPTG induced BL21 (DE3) cells transformed with the respective plasmids. Mutant strains were grown in LB/Amp media and induced with IPTG at OD600 = 0.6. Protein purification was carried out on a cation exchange column CM 16/10 (Amersham Biosciences) in 10 mM sodium borate buffer and eluted with NaCl gradient (0–300 mM). Buffer exchange and additional protein purification were performed on a Superdex 200 size exclusion column (Amersham Biosciences). Purified colicin E1 histidine mutants were digested with thermolysin (1:150 protein to protease molar ratio) in 1 M NaCl, 50 mM Tris pH 8.0, overnight at room temperature. The reaction was terminated by EDTA addition. Proteolysed peptides were purified on a Superdex-75 size exclusion column (Amersham Biosciences) in 20 mM Tris, pH 8.0, 0.1 M NaCl.

2.2. Planar bilayer membranes

Planar BLMs were formed from a 2% solution of lipid in squalene or decane by the brush technique [21] on a 0.55-mm diameter hole in a Teflon partition separating two compartments of a cell containing aqueous solutions of 120 mM KCl, 10 mM MES, 10 mM β-alanine, at pH 4.0 (unless otherwise stated). The electrical current (I) was measured with an amplifier (Keithley 428, Keithley Instruments), digitized with a LabPC 1200 (National Instruments, Austin, TX) and analyzed using a personal computer with the help of WinWCP Strathclyde Electrophysiology Software designed by J. Dempster (University of Strathclyde, UK). A voltage of 60 mV (unless otherwise stated) was applied to BLM with Ag–AgCl electrodes placed directly in the two cell chambers. The shift in the pH of the membrane-bathing solution was performed by the addition of a pre-determined volume of KOH solution to a stirred solution.

3. Results

3.1. pH-shift-induced stimulation of macroscopic current

Colicin E1 and its *C*-terminal channel domain (P178) bind effectively to lipid membranes at pH<5 and induce a voltage-gated transmembrane ionic current [22,23]. Remarkably, the current induced by insertion of P178 into membranes at pH 4 increased dramatically after a subsequent shift in the pH from 4 to 6 (Fig. 1A, curve 1), if the membrane was formed of lipids containing anionic groups (100% DPhPG). The pronounced effect of alkalinization was observed only if the pH of the bathing solution was increased on both sides of the membrane (Fig. 1B, C). This alkalinization did not produce any effect on the conductance of a colicin-free membrane (data not shown).

3.2. Acidic lipid requirement

The two-sided pH shift had no effect on the P178-mediated current (Fig. 1A, curve 2), if the membrane was formed of neutral lipid (DPhPC). If prior to P178 addition, an uncharged membrane

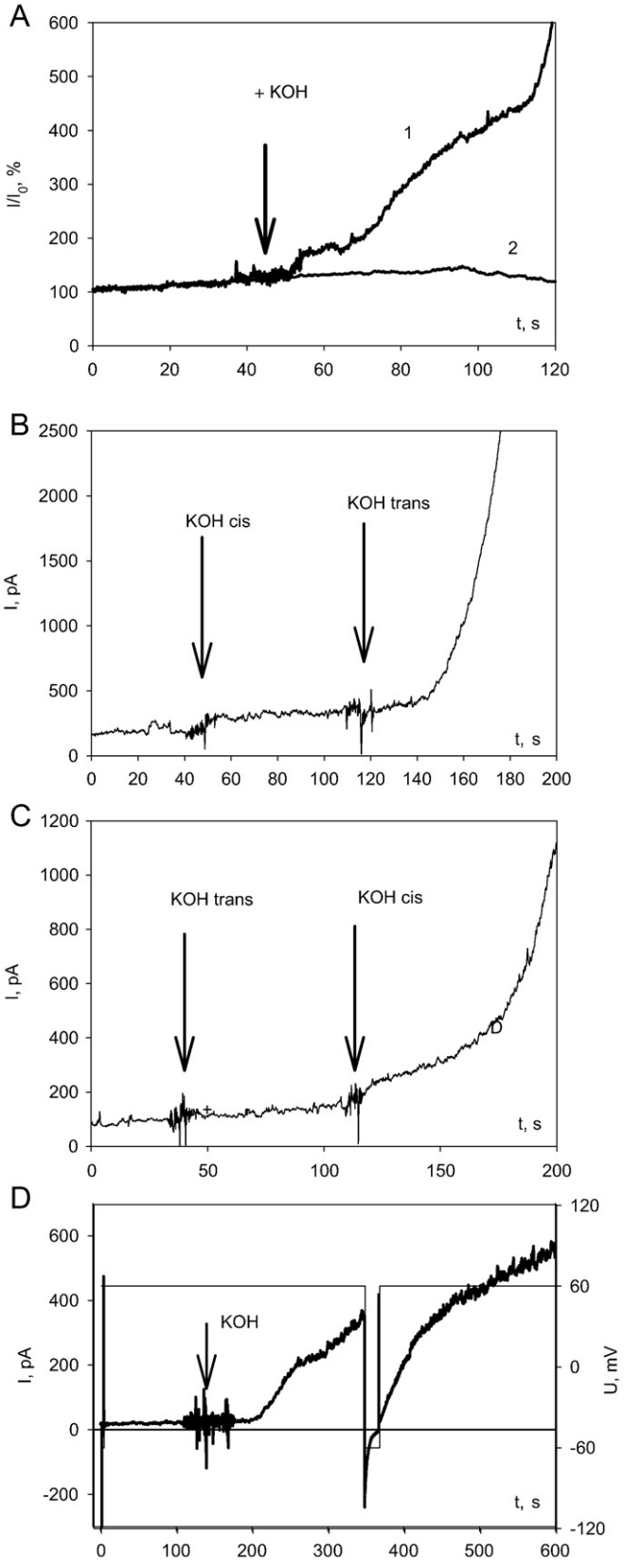

Fig. 1. (A) Effect of a two-sided shift in the pH of the membrane-bathing solution from 4 to 6 on the P178-mediated electric current across a planar bilayer lipid membrane formed from DPhPG (curve 1) and DPhPC (curve 2) dissolved in squalene. pH, 4; voltage, +60 mV. (B, C) Effect of a one-sided shift in the pH of the membrane-bathing solution from 4 to 6 on the P178-mediated electric current across a planar bilayer lipid membrane formed from DPhPG. In B the pH is shifted at first only at the *cis*-side and in C — at first only at the *trans*-side. D. Effect of a two-sided shift in the pH of the membrane-bathing solution from 4 to 6 on the P178-mediated electrical current across a planar bilayer lipid membrane modified by SDS (10 μM in the buffer solution). The BLM voltage was switched as shown. The membrane was formed from DPhPC dissolved in decane. The bathing solution contained 0.12 M KCl, 10 mM MES, 10 mM β-alanine.

containing neutral lipid was preincubated with negatively charged SDS (10 μM; cmc, 8 mM), the increase in the P178-mediated current after the two-sided pH shift was also observed (Fig. 1D). This result not only highlighted the role of membrane charge in the pH-shift effect on the colicin activity, but also excluded the possibility that this effect is due to deprotonation of membrane lipids. The characteristic voltage dependence of the colicin-induced current was retained after the alkalinization-induced stimulation (see Fig. 1D).

It has been shown that the P178 channel-forming activity is strongly dependent on the membrane content of acidic lipids being maximal at 20–30% [12]. The steady-state value of the current reached after the pH shift as compared to the initial value measured before the potassium hydroxide addition was 5.8 ± 1.2 ($n = 3$)times higher and 8.2 ± 2.1 ($n = 3$) times higher, respectively, with BLM containing 10% and 20% DOPG. In agreement with earlier studies (12), induction of the current in the membranes containing a mixture of anionic and neutral lipid required lower concentrations of P178 compared to BLM formed solely of DPhPC or DPhPG.

3.3. Role of histidine 440

In search of amino acid residues that are responsible for the pH-shift effect, we performed experiments with channel-forming domains of colicin mutants where one or both histidine residues of P178 were replaced by alanine. As seen from Fig. 2A, there was no current increase after the pH shift from 4 to 6 with the H440A mutant protein in contrast to the dramatic stimulation of the current observed under these conditions with the wild-type P178 and the H427A mutant (data not shown). The mutation of both histidines (440 and 427) to alanine also resulted in the complete abolishment of the alkalinization effect on the colicin current (data not shown). Thus, His440 is apparently responsible for the alkalinization-induced activation of colicin E1 channels. It is of importance that the H440A mutant displayed much more effective channel formation at pH 4 than the wild-type protein (Fig. 2B). Taking into account the pK value of histidine (~6), it seems rationale to probe the effect of the pH shift on the colicin channel activity in the more extended pH range. Actually, upon the two-sided shift in pH from 6 to 8, we also observed an increase in the P178-induced current across BLM containing 100% DPhPG (data not shown), though the effect was essentially smaller than that produced by the pH shift from 4 to 6. For the reasons of maintaining membrane stability, we did not perform experiments with the shift in pH from 4 to 8.

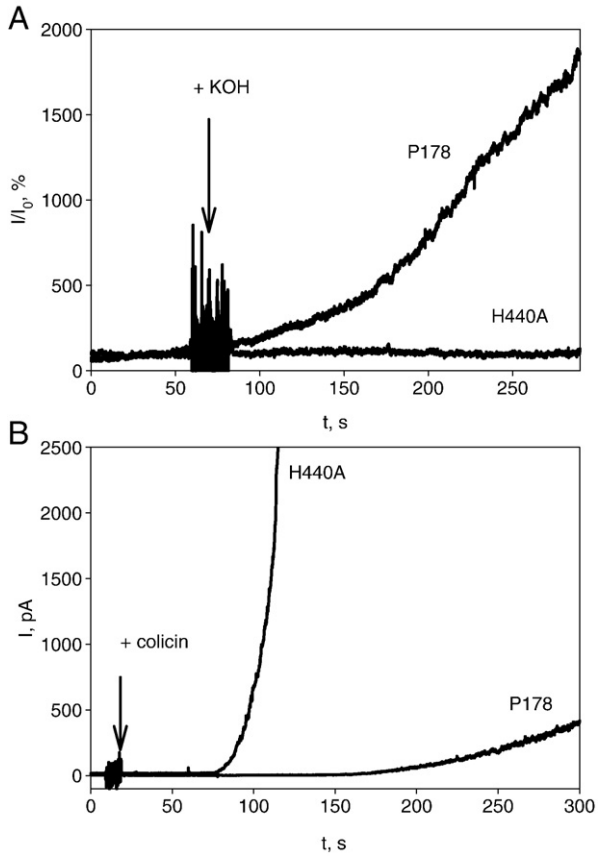

Fig. 2. (A) Effect of a two-sided shift in the pH of the membrane-bathing solution from 4 to 6 on the P178-mediated and H440A-mediated electric current across a planar bilayer lipid membrane formed from DPhPG dissolved in decane, pH, 4; voltage, +60 mV. (B) Time courses of a change in electric current across a 30% DPhPG/70% DPhPC membrane induced by the addition of H440A or P178 to the bathing solution containing 10 mM β-alanine, 10 mM MES, 10 mM Tris, 0.12 M KCl, pH, 4; voltage, 60 mV.

3.4. pH shift does not affect single-channel conductance

To ascertain whether the increase in the colicin-mediated transmembrane current after the alkaline-directed pH shift is associated with an increase in the number of open channels or it is due to an increase in the single-channel conductance, the effect of the pH shift on the properties of colicin single channels was examined. Fig. 3A demonstrates a typical single-channel recording of P178 at pH 4 in BLM formed of the mixture of DPhPC/DPhPG (9:1) in decane. In agreement with our earlier data [15], voltage-dependent channels of two types are seen in the recording: large channels with the conductance of 480 pS and small channels with the conductance of 30 pS. The recording shown in Fig. 3B was obtained after the shift in pH from 4 to 6 (to limit the growth of the conductance, the addition of KOH was made when the negative voltage converting channels to the closed state was applied to BLM). It is seen that the pH shift markedly enhanced the single-channel activity, but the values of the single-channel conductance of both large and small channels did not change. The small channels were observed distinctly only at negative voltage (see the insert), while it was impossible to resolve them at positive voltage because of the very high overall channel activity. Thus, the measurements performed at the single-channel level (Fig. 3B) showed that the alkaline-directed pH shift led to an increase in the number of open channels, i.e. in the number of protein molecules that reached the conducting state, but did not affect the single-channel conductance.

A single-channel recording of H440A (Fig. 3C) also revealed two types of channels, large and small. The conductance of the former was close to that of the wild-type channels, whereas the conductance of the latter was about two times smaller than that of P178 [15]. Therefore His440 exerts strong impact on the properties of colicin E1 channels.

4. Discussion

This study describes activation of colicin channels by an alkaline-directed pH shift, which strictly required a negatively charged membrane (Fig. 1A). It was observed with membranes containing 100% DPhPG, or with a reduced anionic lipid content (Fig. 3B), but was absent in membranes formed of the neutral lipid (100% DPhPC) unless the latter were rendered negatively charged by the addition of SDS (Fig. 1D). These data imply an electrostatic basis for the phenomenon.

Conversion of the positively charged His440 to a neutral alanine led to disappearance of the pH-shift effect on the colicin channel activity (Fig. 2A). Remarkably, the H427A mutant behaved similarly to the wild-type. Thus, the alkalinization-induced activation of colicin channels can be attributed exclusively to deprotonation of His440. The fact that the H440A mutation had a different effect than the H427A

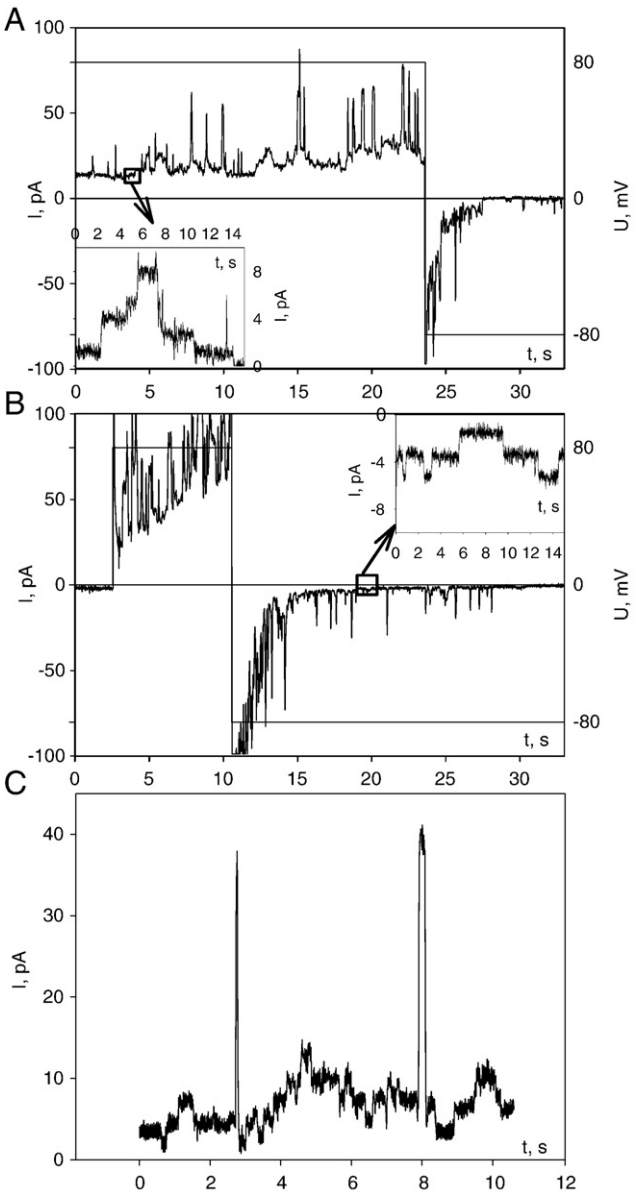

Fig. 3. Single-channel recordings of P178 in a planar bilayer lipid membrane formed from DPhPC/DPhPG (9:1) dissolved in decane at pH 4 (A) and after the shift in pH from 4 to 6 (B). Insert: small channels at the negative voltage. The bathing solution contained 1 M KCl, 10 mM MES, 10 mM Tris, 10 mM β-alanine. The BLM voltage was switched as shown. (C) Single-channel recordings of H440A in a planar bilayer lipid membrane formed from DPhPC dissolved in decane at pH 4. Voltage, +80 mV.

mutation can be explained by specific interaction between the positively charged His440 and acidic lipid head groups that hinders the channel opening. This specific interaction is apparently associated with location of His440 near the lipid head groups in contrast to His427 residing in the V helix that is translocated to the trans-side of the membrane in the open channel state (Fig. 4) [24].

The strict requirement of acidic lipids for the alkalinization-induced colicin activation in combination with the data on the colicin mutants pointed to the crucial role of electrostatic attraction between positively charged histidine residues and negatively charged lipids in this phenomenon. Actually, the conventional scheme of colicin E1 channel formation implies that His440 is translocated to the *trans*-side of the membrane in the open channel state (Fig. 4) [24], though there is a controversy in the literature concerning the role of this residue in the colicin voltage gating [25–27]. It is generally accepted that in the closed channel state (Fig. 4B, upper), helices VIII and IX of P178 bound to the membrane form a hydrophobic hairpin inserted into membrane [27]. According to [12], the strong electrostatic attraction between the positively charged P178 and the negatively charged membrane, restricts the protein flexibility, thereby impeding both the insertion of certain α-helices (presumably II, VI, VII) into a membrane, i.e. their transition from parallel to the membrane to trans-membrane orientation, and the translocation of the other (III–V) α-helices from *cis*- to *trans*-side of the membrane (Fig. 4B, lower). Weakening of the electrostatic interaction upon histidine deprotonation should facilitate the formation of the open channel state.

The fact that the channel-forming activity of H440A at pH 4 is significantly enhanced as compared to the wild-type protein (Fig. 2B) can be explained in terms of our hypothesis by removal of the specific electrostatic interaction between the positively charged His440 residue of the bound colicin molecule and negatively charged lipid head groups that enhances the protein flexibility needed for the channel opening [12]. Earlier data on the marked stimulation of colicin E1 channel activity by chemical modification of histidine residues [28] also support this inference.

The channel state of colicin E1 was shown to be closely related to a toroidal pore [13] which is formed by alpha-helices of the protein and phospholipids, i.e. a mixed protein–lipid pore. It can be concluded that the alkaline-directed pH shift stimulates the transition of bound colicin into a channel state which according to the toroidal pore structure, involves a change in predominant orientation of α-helices from parallel to the membrane (two-dimensional helical array [29,3]) to trans-membrane (toroidal form). It is of interest that depending on the amino acid composition (most likely on the kind of charged residues), alkalinization can either favor (His-containing peptides,

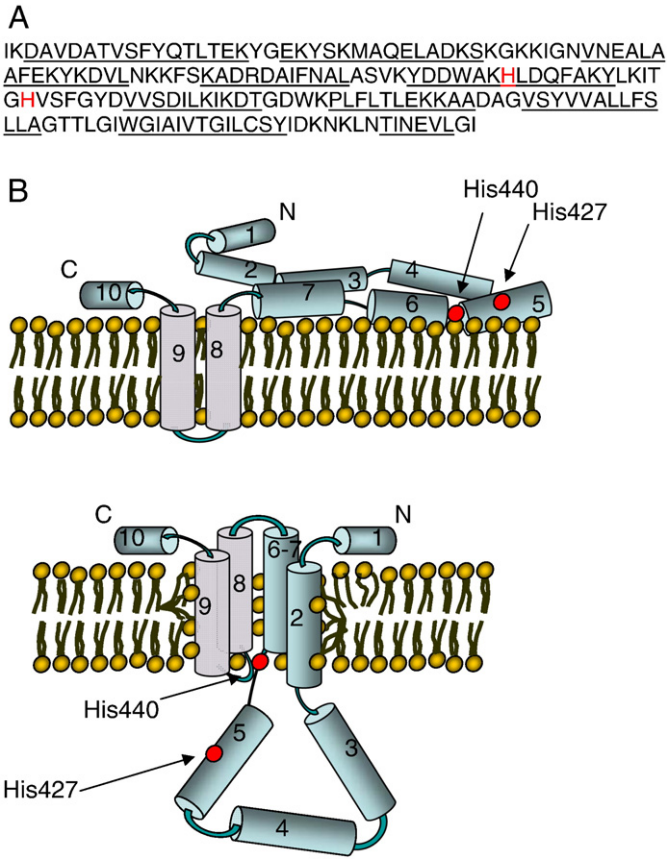

Fig. 4. (A) Sequence alignment of the colicin E1 channel-forming domain with underlined positions of α-helices according to [42]. (B) Putative structure of membrane-bound colicin E1 (P178) in the closed (upper) and open (lower) channel state. Histidines are marked in red.

[30]), or suppress (Asp-containing peptides, [31]) the trans-membrane orientation of α-helices. The pattern of pH dependence of colicin channel formation obtained in the present study points to a crucial role of cationic amino acids in the conformational change of α-helices forming the toroidal structure.

The finding of a large increase in channel-forming activity provoked by an increase in pH with colicin E1 can be related to the phenomenon of an electrostatic arrest of positively charged peptides at the membrane interface observed earlier with melittin [32–37] and cecropin B [38,39]. It was suggested that, as binding affinity increases, the cationic peptides might be inhibited from penetrating the lipid bilayer. With the cell penetrating ribonuclease colicin E3, it was speculated that the apparent weakening of the interaction upon lowering the negatively charged lipid content may reflect a need for the protein to be destabilized but not bound tightly to the membrane for successful translocation across the bilayer [40]. The results obtained with the insecticidal crystal (Cry) pore-forming protein, Cry1Ab toxin, suggest that a more flexible conformation of the toxin could be necessary for membrane insertion, in particular, a looser conformation of the membrane-inserted domain induced by neutral or alkaline pH correlated with active channel formation [41]. It should be noted that stimulation of the conductance by *trans*-side alkalinization was also observed with the B fragment of diphtheria toxin [5].

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